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## Shared Genetic Risk between Eating Disorder- and Substance-Use-Related Phenotypes: Evidence from Genome-Wide Association Studies

Melissa A. Munn-Chernoff<sup>1</sup>, Emma C. Johnson<sup>2</sup>, Yi-Ling Chou<sup>2</sup>, Jonathan R.I. Coleman<sup>3,4</sup>, Laura M. Thornton<sup>1</sup>, Raymond K. Walters<sup>5,6</sup>, Zeynep Yilmaz<sup>1,7</sup>, Jessica H. Baker<sup>1</sup>, Christopher Hübel<sup>3,8</sup>, Scott Gordon<sup>9</sup>, Sarah E. Medland<sup>9</sup>, Hunna J. Watson<sup>1,10,11</sup>, Héléna A. Gaspar<sup>3,4</sup>, Julien Bryois<sup>8</sup>, Anke Hinney<sup>12</sup>, Virpi M. Leppä<sup>8</sup>, Manuel Mattheisen<sup>13,14,15,16</sup>, Stephan Ripke<sup>5,6,17</sup>, Shuyang Yao<sup>8</sup>, Paola Giusti-Rodríguez<sup>7</sup>, Ken B. Hanscombe<sup>18</sup>, Roger A.H. Adan<sup>19,20,21</sup>, Lars Alfredsson<sup>22</sup>, Tetsuya Ando<sup>23</sup>, Ole A. Andreassen<sup>24</sup>, Wade H. Berrettini<sup>25</sup>, Ilka Boehm<sup>26</sup>, Claudette Boni<sup>27</sup>, Vesna Boraska Perica<sup>28,29</sup>, Katharina Buehren<sup>30</sup>, Roland Burghardt<sup>31</sup>, Matteo Cassina<sup>32</sup>, Sven Cichon<sup>33,34,35</sup>, Maurizio Clementi<sup>32</sup>, Roger D. Cone<sup>36</sup>, Philippe Courtet<sup>37</sup>, Scott Crow<sup>38</sup>, James J. Crowley<sup>7,14</sup>, Unna N. Danner<sup>39</sup>, Oliver S.P. Davis<sup>40,41</sup>, Martina de Zwaan<sup>42</sup>, George Dedoussis<sup>43</sup>, Daniela Degortes<sup>44</sup>, Janiece E. DeSocio<sup>45</sup>, Danielle M. Dick<sup>46,47,48</sup>, Dimitris Dikeos<sup>49</sup>, Christian Dina<sup>50</sup>, Monika Dmitrzak-Weglarz<sup>51</sup>, Elisa Docampo<sup>52,53,54</sup>, Laramie E. Duncan<sup>55</sup>, Karin Egberts<sup>56</sup>, Stefan Ehrlich<sup>26</sup>, Geòrgia Escaramís<sup>52,53,54</sup>, Tõnu Esko<sup>57,58</sup>, Xavier Estivill<sup>52,53,54,59</sup>, Anne Farmer<sup>3</sup>, Angela Favaro<sup>44</sup>, Fernando Fernández-Aranda<sup>60,61</sup>, Manfred M. Fichter<sup>62,63</sup>, Krista Fischer<sup>57</sup>, Manuel Föcker<sup>64</sup>, Lenka Foretova<sup>65</sup>, Andreas J. Forstner<sup>66,67,68,34</sup>, Monica Forzan<sup>32</sup>, Christopher S. Franklin<sup>28</sup>, Steven Gallinger<sup>69</sup>, Ina Giegling<sup>70</sup>, Johanna Giuranna<sup>71</sup>, Fragiskos Gonidakis<sup>72</sup>, Philip Gorwood<sup>73,74</sup>, Monica Gratacos Mayora<sup>52,53,54</sup>, Sébastien Guillaume<sup>37</sup>, Yiran Guo<sup>75</sup>, Hakon Hakonarson<sup>75,76</sup>, Konstantinos Hatzikotoulas<sup>77,28</sup>, Joanna Hauser<sup>78</sup>, Johannes Hebebrand<sup>12</sup>, Sietske G. Helder<sup>3,79</sup>, Stefan Herms<sup>33,34</sup>, Beate Herpertz-Dahlmann<sup>30</sup>, Wolfgang Herzog<sup>80</sup>, Laura M. Huckins<sup>28,81</sup>, James I. Hudson<sup>82</sup>, Hartmut Imgart<sup>83</sup>, Hidetoshi Inoko<sup>84</sup>, Vladimir Janout<sup>85</sup>, Susana Jiménez-Murcia<sup>60,61</sup>, Antonio Julià<sup>86</sup>, Gursharan Kalsi<sup>3</sup>, Deborah Kaminská<sup>87</sup>, Leila Karhunen<sup>88</sup>, Andreas Karwautz<sup>89</sup>, Martien JH. Kas<sup>19,90</sup>, James L. Kennedy<sup>91,92,93</sup>, Anna Keski-Rahkonen<sup>94</sup>, Kirsty Kiezebrink<sup>95</sup>, Youl-Ri Kim<sup>96</sup>, Kelly L. Klump<sup>97</sup>, Gun Peggy S. Knudsen<sup>98</sup>, Maria C. La Via<sup>1</sup>, Stephanie Le Hellard<sup>99,100,101</sup>, Robert D. Levitan<sup>92</sup>, Dong Li<sup>75</sup>, Lisa Lilienfeld<sup>102</sup>, Bochao Danae Lin<sup>19</sup>, Jolanta Lissowska<sup>103</sup>, Jurjen Luykx<sup>19</sup>, Pierre J. 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Ophoff<sup>121,122</sup>, Leonid Padyukov<sup>123</sup>, Aarno Palotie<sup>58,124,125</sup>, Jacques Pantel<sup>27</sup>, Hana Papezova<sup>87</sup>, Dalila Pinto<sup>81</sup>, Raquel Rabionet<sup>126,127,128</sup>, Anu Raevuori<sup>94</sup>, Nicolas Ramoz<sup>27</sup>, Ted Reichborn-Kjennerud<sup>98,129</sup>, Valdo Ricca<sup>130</sup>, Samuli Ripatti<sup>131</sup>, Franziska Ritschel<sup>26,132</sup>, Marion Roberts<sup>3</sup>, Alessandro Rotondo<sup>133</sup>, Dan Rujescu<sup>70</sup>, Filip Rybakowski<sup>134</sup>, Paolo Santonastaso<sup>135</sup>, André Scherag<sup>136</sup>, Stephen W. Scherer<sup>137,138</sup>, Ulrike Schmidt<sup>139</sup>, Nicholas J. Schork<sup>140</sup>, Alexandra Schosser<sup>141</sup>, Jochen Seitz<sup>30</sup>, Lenka Slachtova<sup>142</sup>, P. Eline Slagboom<sup>143</sup>, Margarita CT. Slof-Op 't Landt<sup>144,145</sup>, Agnieszka Slopian<sup>146</sup>, Sandro Sorbi<sup>119,147</sup>, Beata Świątkowska<sup>148</sup>, Jin P. 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<sup>1</sup>Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, <sup>2</sup>Department of Psychiatry, Washington University School of Medicine, Saint Louis, Missouri, USA, <sup>3</sup>Institute of Psychiatry, Psychology and Neuroscience, Social, Genetic and Developmental Psychiatry (SGDP) Centre, King's College London, London, UK, <sup>4</sup>National Institute for Health Research Biomedical Research Centre, King's College London and South London and Maudsley National Health Service Trust, London, UK, <sup>5</sup>Analytic and Translational Genetics Unit, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA, <sup>6</sup>Stanley Center for Psychiatric Research, Broad Institute of the Massachusetts Institute of Technology and Harvard University, Cambridge, Massachusetts, USA, <sup>7</sup>Department of Genetics, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, <sup>8</sup>Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden, <sup>9</sup>QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia, <sup>10</sup>School of Psychology, Curtin University, Perth, Western Australia, Australia, <sup>11</sup>School of Paediatrics and Child Health, University of Western Australia, Perth, Western Australia, Australia, <sup>12</sup>Department of Child and Adolescent Psychiatry, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, <sup>13</sup>Department of Biomedicine, Aarhus University, Aarhus, Denmark, <sup>14</sup>Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, <sup>15</sup>Center for Psychiatry Research, Stockholm Health Care Services, Stockholm City Council, Stockholm, Sweden, <sup>16</sup>Department of Psychiatry, Psychosomatics and Psychotherapy, University of Würzburg, Würzburg, Germany, <sup>17</sup>Department of Psychiatry and Psychotherapy, Charité - Universitätsmedizin, Berlin, Germany, <sup>18</sup>Department of Medical and Molecular Genetics, King's College London, Guy's Hospital, London, UK, <sup>19</sup>Brain Center Rudolf Magnus, Department of Translational Neuroscience, University Medical Center Utrecht, Utrecht, The Netherlands, <sup>20</sup>Center for Eating Disorders Rintveld, Altrecht Mental Health Institute, Zeist, The Netherlands, <sup>21</sup>Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, <sup>22</sup>Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden, <sup>23</sup>Department of Behavioral Medicine, National Institute of Mental Health, National Center of Neurology and Psychiatry, Kodaira, Tokyo, Japan, <sup>24</sup>NORMENT Centre, Division of Mental Health and Addiction, University of Oslo, Oslo University Hospital, Oslo, Norway, <sup>25</sup>Department of Psychiatry, Center for Neurobiology and Behavior, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA, <sup>26</sup>Division of Psychological and Social Medicine and Developmental Neurosciences, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany, <sup>27</sup>INSERM U894, Centre of Psychiatry and Neuroscience, Paris, France, <sup>28</sup>Wellcome Sanger Institute, Wellcome Genome Campus, Hinxton, Cambridge, UK, <sup>29</sup>Department of Medical Biology, School of Medicine, University of Split, Split, Croatia, <sup>30</sup>Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, RWTH Aachen University, Aachen, Germany, <sup>31</sup>Klinikum Frankfurt/Oder, Frankfurt, Germany, <sup>32</sup>Clinical Genetics Unit, Department of Woman and Child Health, University of Padova, Padova, Italy, <sup>33</sup>Institute of Medical Genetics and Pathology, University Hospital Basel, Basel, Switzerland, <sup>34</sup>Department of Biomedicine, University of Basel, Basel, Switzerland, <sup>35</sup>Institute of Neuroscience and Medicine (INM-1), Research Center Juelich, Juelich, Germany, <sup>36</sup>Life Sciences Institute and Department of Molecular and Integrative Physiology, University of Michigan, Ann Arbor, Michigan, USA, <sup>37</sup>Department of Emergency

Psychiatry and Post-Acute Care, CHRU Montpellier, University of Montpellier, Montpellier, France, <sup>38</sup>Department of Psychiatry, University of Minnesota, Minneapolis, Minnesota, USA, <sup>39</sup>Altrecht Eating Disorders Rintveld, Altrecht Mental Health Institute, Zeist, The Netherlands, <sup>40</sup>MRC Integrative Epidemiology Unit, University of Bristol, Bristol, UK, <sup>41</sup>School of Social and Community Medicine, University of Bristol, Bristol, UK, <sup>42</sup>Department of Psychosomatic Medicine and Psychotherapy, Hannover Medical School, Hannover, Germany, <sup>43</sup>Department of Nutrition and Dietetics, Harokopio University, Athens, Greece, <sup>44</sup>Department of Neurosciences, University of Padova, Padova, Italy, <sup>45</sup>College of Nursing, Seattle University, Seattle, Washington, USA, <sup>46</sup>Department of Psychology, Virginia Commonwealth University, Richmond, Virginia, USA, <sup>47</sup>College Behavioral and Emotional Health Institute, Virginia Commonwealth University, Richmond, Virginia, USA, <sup>48</sup>Department of Human & Molecular Genetics, Virginia Commonwealth University, Richmond, Virginia, USA, <sup>49</sup>Department of Psychiatry, Athens University Medical School, Athens University, Athens, Greece, <sup>50</sup>l'institut du thorax, INSERM, CNRS, Univ Nantes, Nantes, France, <sup>51</sup>Department of Psychiatric Genetics, Poznan University of Medical Sciences, Poznan, Poland, <sup>52</sup>Barcelona Institute of Science and Technology, Barcelona, Spain, <sup>53</sup>Universitat Pompeu Fabra, Barcelona, Spain, <sup>54</sup>Centro de Investigación Biomédica en Red en Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain, <sup>55</sup>Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, California, USA, <sup>56</sup>Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University Hospital of Würzburg, Centre for Mental Health, Würzburg, Germany, <sup>57</sup>Estonian Genome Center, University of Tartu, Tartu, Estonia, <sup>58</sup>Program in Medical and Population Genetics, Broad Institute of the Massachusetts Institute of Technology and Harvard University, Cambridge, Massachusetts, USA, <sup>59</sup>Genomics and Disease, Bioinformatics and Genomics Programme, Centre for Genomic Regulation, Barcelona, Spain, <sup>60</sup>Department of Psychiatry, University Hospital of Bellvitge –IDIBELL and CIBERobn, Barcelona, Spain, <sup>61</sup>Department of Clinical Sciences, School of Medicine, University of Barcelona, Barcelona, Spain, <sup>62</sup>Department of Psychiatry and Psychotherapy, Ludwig-Maximilians-University, Munich, Germany, <sup>63</sup>Schön Klinik Roseneck affiliated with the Medical Faculty of the University of Munich, Munich, Germany, <sup>64</sup>Department of Child and Adolescent Psychiatry, University of Münster, Münster, Germany, <sup>65</sup>Department of Cancer, Epidemiology and Genetics, Masaryk Memorial Cancer Institute, Brno, Czech Republic, <sup>66</sup>Centre for Human Genetics, University of Marburg, Marburg, Germany, <sup>67</sup>Institute of Human Genetics, University of Bonn, School of Medicine & University Hospital Bonn, Bonn, Germany, <sup>68</sup>Department of Psychiatry (UPK), University of Basel, Basel, Switzerland, <sup>69</sup>Department of Surgery, Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada, <sup>70</sup>Department of Psychiatry, Psychotherapy and Psychosomatics, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany, <sup>71</sup>Department of Child and Adolescent Psychiatry, University Hospital Essen, University of Duisburg-Essen, Essen, Germany, <sup>72</sup>1st Psychiatric Department, National and Kapodistrian University of Athens, Medical School, Eginition Hospital, Athens, Greece, <sup>73</sup>INSERM U1266, Institute of Psychiatry and Neuroscience of Paris, Paris, France, <sup>74</sup>CMME (GHU Paris Psychiatrie et Neurosciences), Paris Descartes University, Paris, France, <sup>75</sup>Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, <sup>76</sup>Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia,

Pennsylvania, USA, <sup>77</sup>Institute of Translational Genomics, Helmholtz Zentrum München - German Research Centre for Environmental Health, Neuherberg, Germany, <sup>78</sup>Department of Adult Psychiatry, Poznan University of Medical Sciences, Poznan, Poland, <sup>79</sup>Zorg op Orde, Delft, The Netherlands, <sup>80</sup>Department of General Internal Medicine and Psychosomatics, Heidelberg University Hospital, Heidelberg University, Heidelberg, Germany, <sup>81</sup>Department of Psychiatry, and Genetics and Genomics Sciences, Division of Psychiatric Genomics, Icahn School of Medicine at Mount Sinai, New York, New York, USA, <sup>82</sup>Biological Psychiatry Laboratory, McLean Hospital/Harvard Medical School, Boston, Massachusetts, USA, <sup>83</sup>Eating Disorders Unit, Parklandklinik, Bad Wildungen, Germany, <sup>84</sup>Department of Molecular Life Science, Division of Basic Medical Science and Molecular Medicine, School of Medicine, Tokai University, Isehara, Japan, <sup>85</sup>Faculty of Health Sciences, Palacky University, Olomouc, Czech Republic, <sup>86</sup>Rheumatology Research Group, Vall d'Hebron Research Institute, Barcelona, Spain, <sup>87</sup>Department of Psychiatry, First Faculty of Medicine, Charles University, Prague, Czech Republic, <sup>88</sup>Institute of Public Health and Clinical Nutrition, Department of Clinical Nutrition, University of Eastern Finland, Kuopio, Finland, <sup>89</sup>Eating Disorders Unit, Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria, <sup>90</sup>Groningen Institute for Evolutionary Life Sciences, University of Groningen, Groningen, The Netherlands, <sup>91</sup>Centre for Addiction and Mental Health, Toronto, Ontario, Canada, <sup>92</sup>Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada, <sup>93</sup>Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada, <sup>94</sup>Department of Public Health, University of Helsinki, Helsinki, Finland, <sup>95</sup>Institute of Applied Health Sciences, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, UK, <sup>96</sup>Department of Psychiatry, Seoul Paik Hospital, Inje University, Seoul, Korea, <sup>97</sup>Department of Psychology, Michigan State University, East Lansing, Michigan, USA, <sup>98</sup>Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway, <sup>99</sup>Department of Clinical Science, Norwegian Centre for Mental Disorders Research (NORMENT), University of Bergen, Bergen, Norway, <sup>100</sup>Dr. Einar Martens Research Group for Biological Psychiatry, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, Norway, <sup>101</sup>Department of Clinical Medicine, Laboratory Building, Haukeland University Hospital, Bergen, Norway, <sup>102</sup>The Chicago School of Professional Psychology, Washington DC Campus, USA, <sup>103</sup>Department of Cancer Epidemiology and Prevention, M Skłodowska-Curie Cancer Center - Oncology Center, Warsaw, Poland, <sup>104</sup>BESE Division, King Abdullah University of Science and Technology, Thuwal, Saudi Arabia, <sup>105</sup>Department of Psychiatry, University of Lausanne-University Hospital of Lausanne (UNIL-CHUV), Lausanne, Switzerland, <sup>106</sup>Department of Psychiatry, University of Campania "Luigi Vanvitelli", Naples, Italy, <sup>107</sup>Center for Integrative Genomics, University of Lausanne, Lausanne, Switzerland, <sup>108</sup>Department of Paediatric Laboratory Medicine, Division of Genome Diagnostics, The Hospital for Sick Children, Toronto, Ontario, Canada, <sup>109</sup>NORMENT KG Jebsen Centre, Division of Mental Health and Addiction, University of Oslo, Oslo University Hospital, Oslo, Norway, <sup>110</sup>Department of Psychiatry, University College Cork, Cork, Ireland, <sup>111</sup>Eist Linn Adolescent Unit, Bessborough, Health Service Executive South, Cork, Ireland, <sup>112</sup>Institute of Molecular and Cell Biology, University of Tartu, Tartu, Estonia, <sup>113</sup>Molecular Epidemiology Section (Department of Biomedical Datasciences), Leiden University Medical Centre, Leiden, The Netherlands, <sup>114</sup>Department of Psychiatry, Faculty of Medicine, University

of Geneva, Geneva, Switzerland, <sup>115</sup>Division of Child and Adolescent Psychiatry, Geneva University Hospital, Geneva, Switzerland, <sup>116</sup>National Center for PTSD, VA Boston Healthcare System, Boston, Massachusetts, USA, <sup>117</sup>Department of Psychiatry, Boston University School of Medicine, Boston, Massachusetts, USA, <sup>118</sup>Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy, <sup>119</sup>Department of Neuroscience, Psychology, Drug Research and Child Health (NEUROFARBA), University of Florence, Florence, Italy, <sup>120</sup>Kartini Clinic, Portland, Oregon, USA, <sup>121</sup>Center for Neurobehavioral Genetics, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, California, USA, <sup>122</sup>Department of Psychiatry, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands, <sup>123</sup>Division of Rheumatology, Department of Medicine, Center for Molecular Medicine, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden, <sup>124</sup>Institute for Molecular Medicine FIMM, HiLIFE, University of Helsinki, Helsinki, Finland, <sup>125</sup>Center for Human Genome Research, Massachusetts General Hospital, Boston, Massachusetts, USA, <sup>126</sup>Saint Joan de Déu Research Institute, Saint Joan de Déu Barcelona Children's Hospital, Barcelona, Spain, <sup>127</sup>Institute of Biomedicine (IBUB), University of Barcelona, Barcelona, Spain, <sup>128</sup>Department of Genetics, Microbiology and Statistics, University of Barcelona, Barcelona, Spain, <sup>129</sup>Institute of Clinical Medicine, University of Oslo, Oslo, Norway, <sup>130</sup>Department of Health Science, University of Florence, Florence, Italy, <sup>131</sup>Department of Biometry, University of Helsinki, Helsinki, Finland, <sup>132</sup>Eating Disorders Research and Treatment Center, Department of Child and Adolescent Psychiatry, Faculty of Medicine, Technische Universität Dresden, Dresden, Germany, <sup>133</sup>Department of Psychiatry, Neurobiology, Pharmacology, and Biotechnologies, University of Pisa, Pisa, Italy, <sup>134</sup>Department of Psychiatry, Poznan University of Medical Sciences, Poznan, Poland, <sup>135</sup>Department of Neurosciences, Padua Neuroscience Center, University of Padova, Padova, Italy, <sup>136</sup>Institute of Medical Statistics, Computer and Data Sciences, Jena University Hospital, Jena, Germany, <sup>137</sup>Department of Genetics and Genomic Biology, The Hospital for Sick Children, Toronto, Ontario, Canada, <sup>138</sup>McLaughlin Centre, University of Toronto, Toronto, Ontario, Canada, <sup>139</sup>Institute of Psychiatry, Psychology and Neuroscience, Department of Psychological Medicine, King's College London, London, UK, <sup>140</sup>J. Craig Venter Institute (JCVI), La Jolla, California, USA, <sup>141</sup>Department of Psychiatry and Psychotherapy, Medical University of Vienna, Vienna, Austria, <sup>142</sup>Department of Pediatrics and Center of Applied Genomics, First Faculty of Medicine, Charles University, Prague, Czech Republic, <sup>143</sup>Molecular Epidemiology Section (Department of Medical Statistics), Leiden University Medical Centre, Leiden, The Netherlands, <sup>144</sup>Center for Eating Disorders Ursula, Rivierduinen, Leiden, The Netherlands, <sup>145</sup>Department of Psychiatry, Leiden University Medical Centre, Leiden, The Netherlands, <sup>146</sup>Department of Child and Adolescent Psychiatry, Poznan University of Medical Sciences, Poznan, Poland, <sup>147</sup>IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy, <sup>148</sup>Department of Environmental Epidemiology, Nofer Institute of Occupational Medicine, Lodz, Poland, <sup>149</sup>Department of Psychiatry, University of Naples SUN, Naples, Italy, <sup>150</sup>Department of Psychiatry, University of Perugia, Perugia, Italy, <sup>151</sup>Brain Sciences Department, Stremble Ventures, Limassol, Cyprus, <sup>152</sup>Adolescent Health Unit, Second Department of Pediatrics, "P. & A. Kyriakou" Children's Hospital, University of Athens, Athens, Greece, <sup>153</sup>Pediatric Intensive Care Unit, "P. & A. Kyriakou" Children's Hospital, University of Athens,

Athens, Greece, <sup>154</sup>Faculty of Social and Behavioral Sciences, Utrecht University, Utrecht, The Netherlands, <sup>155</sup>Department of Internal Medicine VI, Psychosomatic Medicine and Psychotherapy, University Medical Hospital Tuebingen, Tuebingen, Germany, <sup>156</sup>BioRealm, LLC, Walnut, California, USA, <sup>157</sup>Oregon Research Institute, Eugene, Oregon, USA, <sup>158</sup>Christchurch Health and Development Study, University of Otago, Christchurch, New Zealand, <sup>159</sup>The Center for Eating Disorders at Sheppard Pratt, Baltimore, Maryland, USA, <sup>160</sup>Department of Psychiatry, Weill Cornell Medical College, New York, New York, USA, <sup>161</sup>Eating Recovery Center, Denver, Colorado, USA, <sup>162</sup>Department of Psychiatry, University of California San Diego, La Jolla, California, USA, <sup>163</sup>Department of Psychiatry and Behavioral Science, University of North Dakota School of Medicine and Health Sciences, Fargo, North Dakota, USA, <sup>164</sup>Population Health Department, QIMR Berghofer Medical Research Institute, Brisbane, Queensland, Australia, <sup>165</sup>Biostatistics and Computational Biology Unit, University of Otago, Christchurch, New Zealand, <sup>166</sup>Department of Psychiatry and Biobehavioral Science, Semel Institute for Neuroscience and Human Behavior, University of California Los Angeles, Los Angeles, California, USA, <sup>167</sup>David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, USA, <sup>168</sup>Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark, <sup>169</sup>Centre for Mental Health, University Health Network, Toronto, Ontario, Canada, <sup>170</sup>Program for Eating Disorders, University Health Network, Toronto, Ontario, Canada, <sup>171</sup>The Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH), Aarhus, Denmark, <sup>172</sup>Centre for Integrative Sequencing, iSEQ, Aarhus University, Aarhus, Denmark, <sup>173</sup>Bioinformatics Research Centre, Aarhus University, Aarhus, Denmark, <sup>174</sup>Institute for Molecular Bioscience, University of Queensland, Brisbane, Queensland, Australia, <sup>175</sup>National Centre for Register-Based Research, Aarhus BSS, Aarhus University, Aarhus, Denmark, <sup>176</sup>Centre for Integrated Register-based Research (CIRRAU), Aarhus University, Aarhus, Denmark, <sup>177</sup>Department of Psychological Medicine, University of Otago, Christchurch, New Zealand, <sup>178</sup>Canterbury District Health Board, Christchurch, New Zealand, <sup>179</sup>Department of Pathology and Biomedical Science, University of Otago, Christchurch, New Zealand, <sup>180</sup>Department of Psychiatry and Neurochemistry, Institute of Neuroscience and Physiology, The Sahlgrenska Academy at the University of Gothenburg, Gothenburg, Sweden, <sup>181</sup>Division of Human Genetics, Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut, USA, <sup>182</sup>Veterans Affairs Connecticut Healthcare System, West Haven, Connecticut, USA, <sup>183</sup>Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana, USA, <sup>184</sup>Faculty of Business, Karabuk University, Karabuk, Turkey, <sup>185</sup>Virginia Commonwealth University Alcohol Research Center, Virginia Commonwealth University, Richmond, Virginia, USA, <sup>186</sup>Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, Virginia, USA, <sup>187</sup>Department of Psychiatry, Virginia Commonwealth University, Richmond, Virginia, USA, <sup>188</sup>Psychiatric Genomics and Pharmacogenomics Program, Mayo Clinic, Rochester, Minnesota, USA, <sup>189</sup>Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, New York, USA, <sup>190</sup>Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota, USA, <sup>191</sup>Department of Psychiatry and Psychology, Mayo Clinic, Rochester, Minnesota, USA, <sup>192</sup>Department of Psychiatry and Behavioral Sciences, State University of New York Downstate Medical Center, Brooklyn, New York, USA, <sup>193</sup>Division of Psychiatry,



University of Edinburgh, Edinburgh, UK, <sup>194</sup>Institute of Human Genetics, University of Bonn School of Medicine & University Hospital Bonn, Bonn, Germany, <sup>195</sup>Department of Psychiatry, University of Utah, Salt Lake City, Utah, USA, <sup>196</sup>Department of Genetic Epidemiology in Psychiatry, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, <sup>197</sup>Laboratory of Neurogenetics, NIH/NIAAA, Bethesda, Maryland, USA, <sup>198</sup>Institute of Human Genetics, School of Medicine & University Hospital Bonn, University of Bonn, Bonn, Germany, <sup>199</sup>Human Genomics Research Group, Department of Biomedicine, University of Basel, Basel, Switzerland, <sup>200</sup>Institute of Medical Genetics and Pathology, University Hospital Basel, University Hospital Basel, Basel, Switzerland, <sup>201</sup>Department of Biological Psychology, Amsterdam Public Health Research Institute, Vrije Universiteit Amsterdam, Amsterdam, The Netherlands, <sup>202</sup>Turku Institute for Advanced Studies, University of Turku, Turku, Finland, <sup>203</sup>Department of Psychology and Logopedics, University of Helsinki, Helsinki, Finland, <sup>204</sup>Department of Medical and Molecular Genetics, Indiana University School of Medicine, Indianapolis, Indiana, USA, <sup>205</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland, USA, <sup>206</sup>Division of Psychiatry, Centre for Cognitive Ageing and Cognitive Epidemiology, University of Edinburgh, Edinburgh, UK, <sup>207</sup>Department of Integrative Physiology, University of Colorado Boulder, Boulder, Colorado, USA, <sup>208</sup>Department of Psychiatry and Behavioral Sciences, Henri Begleiter Neurodynamics Laboratory, SUNY Downstate Medical Center, Brooklyn, New York, USA, <sup>209</sup>Department of Psychiatry, Amsterdam Public Health Research Institute, VU University Medical Center/GGz inGeest, Amsterdam, The Netherlands, <sup>210</sup>Department of Genetics, Washington University School of Medicine, Saint Louis, Missouri, USA, <sup>211</sup>NIH/NIAAA, Office of the Clinical Director, Bethesda, Maryland, USA, <sup>212</sup>Department of Medicine (Biomedical Genetics), Boston University School of Medicine, Boston, Massachusetts, USA, <sup>213</sup>Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Cambridge, Massachusetts, USA, <sup>214</sup>Department of Sociology, Harvard University, Cambridge, Massachusetts, USA, <sup>215</sup>Department of Pharmacology, University of Colorado School of Medicine, Aurora, Colorado, USA, <sup>216</sup>Institute of Behavioral Science, University of Colorado, Boulder, Colorado, USA, <sup>217</sup>Department of Sociology, University of Colorado, Boulder, Colorado, USA, <sup>218</sup>Department of Molecular Pharmacology and Experimental Therapeutics, Mayo Clinic, Rochester, Minnesota, USA, <sup>219</sup>Department of Psychiatry, University of Vermont Medical Center, Burlington, Vermont, USA, <sup>220</sup>Department of Medicine, Division of Biostatistics, Washington University School of Medicine, Saint Louis, Missouri, USA, <sup>221</sup>Department of Psychiatry, University of Mainz, Mainz, Germany, <sup>222</sup>National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, Australia, <sup>223</sup>Stanford University Graduate School of Education, Stanford University, Stanford, California, USA, <sup>224</sup>Department of Psychiatry and Psychotherapy, University of Düsseldorf, Düsseldorf, Germany, <sup>225</sup>MRC Human Genetics Unit, Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, UK, <sup>226</sup>Max-Planck-Institute of Psychiatry, Munich, Germany, <sup>227</sup>Department of Psychology, University of Minnesota, Minneapolis, Minnesota, USA, <sup>228</sup>Department of Addictive Behavior and Addiction Medicine, Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany, <sup>229</sup>Department of Psychiatry and Psychotherapy, University Hospital, LMU Munich, Munich, Germany, <sup>230</sup>Department of Psychiatry, University of Iowa

Roy J and Lucille A Carver College of Medicine, Iowa City, Iowa, USA, <sup>231</sup>Addictions Department, Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK, <sup>232</sup>Department of Psychiatry, University of Bonn, Bonn, Germany, <sup>233</sup>Department of Public Health Solutions, National Institute for Health and Welfare, Helsinki, Finland, <sup>234</sup>Department of Statistical Genetics, Max-Planck-Institute of Psychiatry, München, Germany, <sup>235</sup>Aberdeen Biomedical Imaging Centre, School of Medicine, Medical Sciences & Nutrition, University of Aberdeen, Foresterhill, Aberdeen, UK, <sup>236</sup>Department of Psychiatry, Indiana University School of Medicine, Indianapolis, Indiana, USA, <sup>237</sup>Department of Psychiatry, Psychotherapy and Psychosomatics, Martin-Luther-University Halle-Wittenberg, Herborn, Germany, <sup>238</sup>Department of Psychiatry and Psychotherapy, Vitos Hospital Herborn, Herborn, Germany, <sup>239</sup>School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, <sup>240</sup>Department of Psychiatry and Psychotherapy, University of Regensburg Psychiatric Health Care Aargau, Regensburg, Germany, <sup>241</sup>LVR-Hospital Essen, Department of Psychiatry and Psychotherapy and Department of Addictive Behaviour and Addiction Medicine, Medical Faculty, University of Duisburg-Essen, Essen, Germany, <sup>242</sup>Medical Park Chiemseeblick in Bernau-Felden, Ludwig-Maximilians-University, Bernau am Chiemsee, Germany, <sup>243</sup>Psychiatric Hospital, Ludwig-Maximilians-University, Bernau am Chiemsee, Germany, <sup>244</sup>Department of Psychiatry and Psychotherapy, University of Regensburg, Regensburg, Germany, <sup>245</sup>Department of Psychiatry, Psychiatric Hospital, Ludwig-Maximilians-University, Munich, Germany, <sup>246</sup>Department of Sociology, University of Utah, Salt Lake City, Utah, USA, <sup>247</sup>Department of Psychology, University of California San Diego, USA, <sup>248</sup>Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, USA, <sup>249</sup>Department of Psychiatry and Behavioral Neuroscience, University of Chicago, Chicago, Illinois, USA, <sup>250</sup>NIAAA Intramural Research Program, Bethesda, Maryland, USA, <sup>251</sup>Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland, <sup>252</sup>National Institute for Health and Welfare, Helsinki, Finland, <sup>253</sup>Department of Neurology, Boston University School of Medicine, Boston, Massachusetts, USA, <sup>254</sup>Department of Ophthalmology, Boston University School of Medicine, Boston, Massachusetts, USA, <sup>255</sup>Department of Epidemiology, School of Public Health, Boston University, Boston, Massachusetts, USA, <sup>256</sup>Department of Biostatistics, School of Public Health, Boston University, Boston, Massachusetts, USA, <sup>257</sup>Office of the Clinical Director, NIH/NIAAA, Bethesda, Maryland, USA, <sup>258</sup>Center for Omics Discovery and Epidemiology, Behavioral Health Research Division, RTI International, Research Triangle Park, North Carolina, USA, <sup>259</sup>Department of Sociology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, <sup>260</sup>Carolina Population Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA, <sup>261</sup>Department of Psychiatry, University of Connecticut School of Medicine, Farmington, Connecticut, USA, <sup>262</sup>Institute for Behavioral Genetics, University of Colorado Boulder, Boulder, Colorado, USA, <sup>263</sup>Department of Psychiatry, University of Colorado Denver, Aurora, Colorado, USA, <sup>264</sup>Fellow Program, RTI International, Research Triangle Park, North Carolina, USA, <sup>265</sup>Center for Studies of Addiction, University of Pennsylvania Perelman School of Medicine, Philadelphia, Pennsylvania, USA, <sup>266</sup>VISN 4 MIRECC, Crescenz VAMC, Philadelphia, Pennsylvania, USA, <sup>267</sup>Department of Molecular, Cellular, and Developmental Biology, University of Colorado Boulder, Boulder, Colorado, USA, <sup>268</sup>Peter Boris Centre for

Addictions Research, McMaster University/St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada, <sup>269</sup>Michael G. DeGroote Centre for Medicinal Cannabis Research, McMaster University/St. Joseph's Healthcare Hamilton, Hamilton, Ontario, Canada, <sup>270</sup>Institute for Genomic Medicine, University of California San Diego, La Jolla, California, USA, <sup>271</sup>Department of Psychiatry, Amsterdam UMC, VU University and GGZinGeest, Amsterdam, The Netherlands, <sup>272</sup>Department of Psychological & Brain Sciences, Indiana University Bloomington, Bloomington, Indiana, USA, <sup>273</sup>School of Pharmacy, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, <sup>274</sup>Department of Biostatistics, Yale School of Public Health, Yale University, New Haven, Connecticut, USA, <sup>275</sup>School of Psychology, Flinders University, Adelaide, South Australia, Australia, <sup>276</sup>Queensland Brain Institute, University of Queensland, Brisbane, Queensland, Australia, <sup>277</sup>Department of Genetics, Yale School of Medicine, New Haven, Connecticut, USA, <sup>278</sup>Department of Neuroscience, Yale School of Medicine, New Haven, Connecticut, USA, <sup>279</sup>Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina, USA

\*Joint last authors

**Correspondence:** Melissa A. Munn-Chernoff, PhD  
Department of Psychiatry  
University of North Carolina at Chapel Hill  
101 Manning Drive, Campus Box 7160  
Chapel Hill, NC 27599  
Phone: 984-974-3788  
Email: [melissa\\_chernoff@med.unc.edu](mailto:melissa_chernoff@med.unc.edu)

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### Abstract

Eating disorders and substance use disorders frequently co-occur. Twin studies reveal shared genetic variance between liabilities to eating disorders and substance use, with the strongest associations between symptoms of bulimia nervosa and problem alcohol use (genetic correlation [ $r_g$ ], twin-based=0.23-0.53). We estimated the genetic correlation between eating disorder and substance use and disorder phenotypes using data from genome-wide association studies (GWAS). Four eating disorder phenotypes (anorexia nervosa [AN], AN *with* binge-eating, AN *without* binge-eating, and a bulimia nervosa factor score), and eight substance-use-related phenotypes (drinks per week, alcohol use disorder [AUD], smoking initiation, current smoking, cigarettes per day, nicotine dependence, cannabis initiation, and cannabis use disorder) from eight studies were included. Significant genetic correlations were adjusted for variants associated with major depressive disorder and schizophrenia. Total study sample sizes per phenotype ranged from ~2,400 to ~537,000 individuals. We used linkage disequilibrium score regression to calculate single nucleotide polymorphism-based genetic correlations between eating disorder- and substance-use-related phenotypes. Significant positive genetic associations emerged between AUD and AN ( $r_g=0.18$ ; false discovery rate  $q=0.0006$ ), cannabis initiation and AN ( $r_g=0.23$ ;  $q<0.0001$ ), and cannabis initiation and AN *with* binge-eating ( $r_g=0.27$ ;  $q=0.0016$ ). Conversely, significant negative genetic correlations were observed between three non-diagnostic smoking phenotypes (smoking initiation, current smoking, and cigarettes per day) and AN *without* binge-eating ( $r_{gs}=-0.19$  to  $-0.23$ ;  $qs<0.04$ ). The genetic correlation between AUD and AN was no longer significant after co-varying for major depressive disorder loci. The patterns of association between eating disorder- and substance-use-related phenotypes highlights the potentially complex and substance-specific relationships among these behaviors.

*Keywords:* eating disorders; substance use; genetic correlation

## **Shared Genetic Risk between Eating Disorder- and Substance-Use-Related Phenotypes: Evidence from Genome-Wide Association Studies**

Well-established phenotypic associations exist between eating disorder and substance use phenotypes, with evidence for specific relations between particular types of eating disorders and substance use disorders. The prevalence of an alcohol use disorder (AUD) is greater among individuals with bulimia nervosa and binge-eating disorder than individuals with anorexia nervosa (AN) or healthy controls.<sup>1,2</sup> Similarly, individuals with bulimia nervosa or binge-eating disorder are at increased risk for smoking, nicotine dependence,<sup>3,4</sup> and cannabis use,<sup>4,5</sup> compared with individuals with AN or healthy controls, though these results are not consistent.<sup>1</sup> Importantly, women with the binge-eating/purging subtype of AN report a higher prevalence of AUD, smoking, nicotine dependence, and cannabis use than women with the restricting subtype of AN.<sup>1,5,6</sup> Thus, binge eating—a transdiagnostic symptom defined as eating a large amount of food in a short period of time while experiencing loss of control—may be a key component of the observed association.

However, prior research has only partially addressed whether binge eating is the critical eating disorder symptom in the comorbidity, especially across different milestones of substance use (i.e., initiation through substance use disorder) and across a variety of substances (i.e., alcohol, nicotine, and cannabis). Elucidating shared sources for these associations is crucial because of the increased morbidity and mortality associated with comorbid presentations<sup>7,8</sup> and because improvements in one disorder may exacerbate (or weaken) symptoms of the other disorder.<sup>9</sup> Refining our understanding of these associations could improve prevention and treatment approaches for these debilitating disorders, their comorbidity, and their sequelae.

Accumulating findings from twin studies implicate shared genetic factors between eating disorder- and substance-use-related phenotypes. The strongest reported association is between bulimia nervosa symptoms (including binge eating) and problem alcohol use, with a genetic correlation ( $r_g$ ) ranging from 0.23 to 0.53.<sup>10</sup> Although there has been less focus on genetic associations between bulimia nervosa symptoms and regular smoking and bulimia nervosa symptoms and illicit drug use disorder, twin-based  $r_g$ s of 0.35 and approximately 0.38, respectively, have been reported.<sup>11,12</sup> Limited information exists regarding whether less problematic aspects of substance use exhibit a significant  $r_g$  with eating disorder phenotypes. The impact of genetic factors influencing this comorbidity may significantly increase once an individual has progressed to problematic alcohol use, as genetic effects are more prominent in problem substance use, such as abuse and dependence, than with the initiation and general use of substances.<sup>13-16</sup> No study has comprehensively examined a range of eating disorder- and substance-use-related phenotypes to determine whether the  $r_g$  varies with different aspects of substance use and whether the  $r_g$  varies depending on the eating disorder and substance examined.

Recent advances in genomic methods allow for an assessment of  $r_g$  using existing genome-wide association study (GWAS) summary statistics. Unlike twin studies, these genome-wide methods allow for use of unrelated cases and controls, typically yielding sample sizes in the tens to hundreds of thousands. One such method, linkage disequilibrium score regression (LDSC),<sup>17,18</sup> estimates single-nucleotide polymorphism (SNP)-based heritability and  $r_g$  between phenotypes. Of particular relevance to low prevalence phenotypes, such as AN, estimation of SNP-based  $r_g$  does not require both phenotypes to be measured in the same individual; thus, independent studies assessing only one phenotype can be jointly examined.

The current study estimated SNP-based genetic correlations ( $r_g$ s) between eating disorder- and substance-use-related phenotypes based upon summary statistics from the largest published eating disorder GWAS and existing GWAS encompassing a range of substance-use-related phenotypes (i.e., alcohol, nicotine, and cannabis), using robust data from twin studies to shape our three hypotheses. First, we hypothesized that the strongest SNP-based  $r_g$  would be between eating disorder phenotypes that have binge eating as a core symptom and alcohol use phenotypes, rather than between eating disorder phenotypes and nicotine- and cannabis-use-related phenotypes.<sup>10</sup> Second, we hypothesized that for binge-eating-related phenotypes, the SNP-based  $r_g$  would be higher when assessing AUD than typical alcohol consumption,<sup>10</sup> since we expected that two problem behaviors are more likely to share genetic risk than a problem behavior (e.g., binge eating) and a normative pattern (e.g., alcohol consumption). Because we have less information from twin studies about genetic associations between liabilities to eating disorders and tobacco (nicotine) and cannabis use-related phenotypes, we do not forward specific hypotheses for these substances. Finally, prior studies document robust genetic associations for major depressive disorder and schizophrenia with both eating disorders and substance-use-related phenotypes.<sup>19-21</sup> We hypothesized that  $r_g$ s between eating disorders and substance use and disorder would be attenuated when accounting for variants associated with major depressive disorder and schizophrenia. Findings from this study will yield important information about the role of genetics in this clinically challenging pattern of comorbidity.<sup>22</sup>



## Method

### Participants

We included summary statistics from two existing GWAS of eating disorder phenotypes where participants were primarily of European ancestry<sup>21,23</sup> and data from individuals of European ancestry from six existing GWAS of substance-use-related phenotypes.<sup>19,20,24-27</sup> The eating disorder phenotypes (**Table 1**) included a diagnosis of AN (which was further parsed into AN *with* binge-eating or AN *without* binge-eating) and a bulimia nervosa factor score derived from the Eating Disorder Examination,<sup>28</sup> a well-established structured clinical interview for eating disorders. We did not examine bulimia nervosa or binge-eating disorder because there are currently no published GWAS for either disorder; thus, the bulimia nervosa factor score represents the closest to a GWAS of bulimia nervosa available. Substance-use-related phenotypes ranged from typical use (e.g., drinks per week, smoking initiation, and cannabis initiation) to substance use disorder (i.e., AUD, nicotine dependence, and cannabis use disorder). Sample sizes for the phenotypes ranged from 2,442 (bulimia nervosa factor score) to 537,349 (drinks per week) individuals. **Table 2** provides individual study details.

### Statistical Analysis

We used LDSC<sup>17,18</sup> to evaluate SNP-based genetic correlations ( $r_g$ ) between samples. This method uses the linkage disequilibrium (LD) structure of the genome to estimate the distribution of effect sizes for individual SNPs as a function of their LD score. Under a polygenic model, causal SNPs are likely to be overrepresented in higher LD score bins (i.e., including additional SNPs in high LD), such that associations with SNPs in these LD bins will make stronger contributions to the phenotypic variation under study. This polygenic distribution of

effect sizes across LD score bins provides an estimate of SNP-based heritability, i.e., the proportion of phenotypic variance that is attributable to the aggregate effects of genome-wide SNPs. The correlation of effect sizes across LD bins between two phenotypes then provides an estimate of SNP-based  $r_g$ .

Genetic correlations range from -1 to +1, where the sign indicates that the same genetic factors are contributing to variation in the target traits in *opposite* or *same* directions, respectively. The LDSC intercept for the genetic covariance provides evidence about sample overlap across two traits. SNPs (MAF>0.01) found in the HapMap3 EUR population were used to calculate LD scores. We used the false discovery rate<sup>29</sup> to correct for multiple testing ( $n=66$  tests;  $q<0.05$ ). Finally, post-hoc analyses examined whether significant differences between two  $r_g$ s existed, using the jackknife procedure implemented through LDSC.<sup>17</sup>

We used GNOVA<sup>30</sup> to stratify significant  $r_g$ s between the eating disorder- and substance-use-related phenotypes into both tissue-specific (for seven broadly-defined tissue classes: brain, cardiovascular, epithelial, gastrointestinal, immune-related, muscular, and “other”) and non-tissue-specific functional regions of the genome. GenoCanyon<sup>31</sup> and GenoSkyline<sup>32,33</sup> annotation methods, which integrate transcriptomic and epigenomic data from ENCODE<sup>34</sup> and Roadmap Epigenomics Project,<sup>35</sup> were used to define functional regions of the genome.

Finally, for significant  $r_g$ s detected in LDSC, multi-trait-based conditional and joint analysis using GWAS summary data (mtCOJO)<sup>36</sup> was used to condition both input GWAS (e.g., AN and AUD) for variants associated with major depressive disorder<sup>37</sup> at  $p<5\times 10^{-7}$  and schizophrenia<sup>38</sup> at  $p<5\times 10^{-8}$ . Because fewer genome-wide significant SNPs were identified for major depressive disorder than schizophrenia, we chose a more lenient  $p$ -value threshold for major depressive disorder to capture a comparable number of SNPs. LDSC was used to compute

$r_g$ s using the resulting genome-wide summary statistics for each trait after separately adjusting for major depressive disorder or schizophrenia variants to examine whether conditioning on either disorder would affect the observed genetic relationships.

## Results

The overall SNP-based heritability for the eating disorder phenotypes ranged from 0.20 to 0.39, whereas the corresponding heritabilities for the substance-use-related phenotypes ranged from 0.03 to 0.35 (**Table S1**). **Figure 1** and **Table S1** show the genetic correlations ( $r_g$ s) between all four eating disorder phenotypes and eight substance-use-related phenotypes. Broadly speaking, there were significant  $r_g$ s across substance-use-related phenotypes, ranging from 0.21 (AUD and cigarettes per day) to 0.70 (drinks per week and AUD). Cannabis initiation risk was not significantly genetically correlated with cigarettes per day or nicotine dependence. For the remaining results, we focus on previously unexplored associations of interest in this study—correlations between eating disorder- and substance-use-related phenotypes. For these associations, the genetic covariance intercepts ranged from -0.03 (standard error [SE]=0.01; AN and cannabis initiation) to 0.01 (SE=0.01; AN and cannabis use disorder), indicating some sample overlap (or low-level confounding) existed,<sup>39</sup> although the LDSC approach parses this overlap from the  $r_g$  estimation.

Significant positive  $r_g$ s were observed for alcohol- and cannabis-use-related phenotypes. First, the  $r_g$  was significant between AN and AUD ( $r_g=0.18$ ; SE=0.05;  $q=0.0006$ ), but not between AN and drinks per week ( $r_g=0.01$ ; SE=0.03;  $q=0.91$ ), suggesting that genetic factors that increase risk for AN also increase risk for AUD, but little evidence exists for shared genetic risk between AN and typical alcohol consumption. These two correlations significantly differed

from each other ( $z$ -score=3.51,  $p$ =0.0005). Intriguingly, there was a significant difference in  $r_g$ s for AN and AUD versus AN *without* binge-eating and AUD ( $z$ -score=2.28,  $p$ =0.02), but not for AN and AUD versus AN *with* binge-eating and AUD ( $z$ -score=0.23,  $p$ =0.82). The genetic covariance estimates between AN and AUD were significant in both functional (corrected  $\rho_g$ =0.01; corrected  $r$ =0.23; corrected  $q$ =0.007) and non-functional categories (corrected  $\rho_g$ =0.01; corrected  $r$ =0.19; corrected  $q$ =0.002; **Table S2**), but not in any specific tissue type. No significant association between the bulimia nervosa factor score, which included items pertaining to both binge eating and compensatory behaviors, and either alcohol-use-related phenotype was observed.

Second, the significant  $r_g$  between AN and cannabis initiation was 0.23 (SE=0.04,  $q$ <0.0001) and the significant  $r_g$  between AN *with* binge-eating and cannabis initiation was 0.27 (SE=0.08,  $q$ =0.0017), indicating that genetic factors that increase the risk for AN may also increase risk for cannabis initiation. However, cannabis initiation was not significantly correlated with the bulimia nervosa factor score ( $r_g$ =0.15, SE=0.18,  $q$ =0.57) or with AN *without* binge-eating ( $r_g$ =0.10, SE=0.08,  $q$ =0.31). No significant associations were observed between any eating disorder phenotype and cannabis use disorder ( $r_g$ s=-0.08-0.23; SEs=0.01;  $q$ s≤0.57). Post-hoc analyses revealed significant differences in the  $r_g$ s for AN and cannabis initiation versus AN and cannabis use disorder ( $z$ -score=2.70,  $p$ =0.01). However, the  $r_g$  between AN *with* binge-eating and cannabis initiation, while significant, was statistically different from the  $r_g$  between AN *with* binge-eating and cannabis use disorder. The genetic covariance estimate between AN *with* binge-eating and cannabis initiation was significant in both functional (corrected  $\rho_g$ =0.01; corrected  $r$ =0.60; corrected  $q$ <0.0001) and non-functional categories (corrected  $\rho_g$ =0.01; corrected  $r$ =0.30; corrected  $q$ =0.004; **Table S3**), but not in any specific tissue type. The genetic covariance

estimate between AN *without* binge-eating and cannabis initiation was only significant in non-functional categories (corrected  $\rho_g=0.01$ ; corrected  $r=0.27$ ; corrected  $q=0.004$ ; **Table S4**).

Conversely, for smoking phenotypes, significant correlations were only observed for the AN *without* binge-eating subtype. Smoking initiation ( $r_g=-0.21$ ,  $SE=0.06$ ,  $q=0.0006$ ), current smoking (referred to as smoking cessation in Liu et al.<sup>20</sup>)<sup>1</sup> ( $r_g=-0.19$ ,  $SE=0.08$ ,  $q=0.03$ ), and cigarettes per day ( $r_g=-0.23$ ,  $SE=0.07$ ,  $q=0.003$ ) were significantly and negatively associated with AN *without* binge-eating. Although the correlation between nicotine dependence and AN *without* binge-eating was in the same direction as the other smoking phenotypes, it was not significant ( $r_g=-0.22$ ,  $SE=0.12$ ,  $q=0.14$ ). The  $r_g$ s for AN diagnosis and each of the three non-diagnostic smoking traits versus AN *without* binge-eating and these same smoking traits all differed significantly from each other (z-scores ranged from -3.22 to -2.11;  $p$ -values $\leq 0.04$ ). The genetic covariance estimate between AN *without* binge-eating and smoking initiation was only significant in the non-functional category (corrected  $\rho_g=-0.01$ ; corrected  $r=-0.17$ ; corrected  $q=0.007$ ; **Table S5**). For AN *without* binge-eating and current smoking, the genetic covariance estimate was significant in both functional (corrected  $\rho_g=-0.01$ ; corrected  $r=-0.32$ ; corrected  $q=0.01$ ) and non-functional categories (corrected  $\rho_g=-0.01$ ; corrected  $r=-0.21$ ; corrected  $q=0.03$ ; **Table S6**). Finally, the genetic covariance estimate between AN *without* binge-eating and cigarettes per day was only significant in the non-functional category (corrected  $\rho_g=-0.02$ ; corrected  $r=-0.35$ ; corrected  $q=0.003$ ; **Table S7**).

After conditioning the AN and AUD GWAS summary statistics for loci associated with major depressive disorder, the positive  $r_g$  between AN and AUD was attenuated ( $r_g=0.07$ ;

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<sup>1</sup> In Liu et al. (2019), the phenotype is noted as “smoking cessation”, where current smokers were coded as 2 and former smokers were coded as 1. Because the comparison group is “current smokers”, we have renamed this phenotype as “current smoking” for clarification and ease of interpretation across all smoking phenotypes.

SE=0.05,  $q=0.125$ ; **Table S8**) and significantly lower than the unadjusted  $r_g$  (z-score=2.48,  $p=0.01$ ). In contrast, after conditioning the AN *with* binge-eating and cannabis initiation GWAS for major depressive disorder, the resulting  $r_g$  was marginally smaller but remained significant after correction for multiple tests ( $r_g=0.21$ , SE=0.08,  $q=0.016$ ). After conditioning for the major depressive disorder GWAS,  $r_g$ s between AN *without* binge-eating and smoking initiation, current smoking, and cigarettes per day remained significant and modestly increased in magnitude ( $r_g$ s=-0.27 to -0.31; SEs=0.05 to 0.09;  $q$ s<0.0009). All  $r_g$ s remained significant after conditioning the AN and substance-use-related phenotypes for schizophrenia ( $r_g$ s=-0.20 to 0.27; SEs=0.04 to 0.08;  $q$ s<0.03; **Table S9**).

## Discussion

Using existing GWAS data, we investigated genetic associations between liabilities to four eating disorder- and eight substance-use-related phenotypes spanning initiation and typical use to substance use disorder. We found differential patterns of association between AN with and without binge-eating and substance-use-related traits, which may point toward substance-specific genetic relationships. Additionally, there may be some degree of symptom overlap contributing to these associations.

Three main patterns emerged. First, in line with prior twin studies, we observed a positive genetic correlation ( $r_g$ ) between problem alcohol use (i.e., AUD) and AN diagnosis. Second, we observed positive, significant  $r_g$ s between cannabis initiation and AN diagnosis, as well as cannabis initiation and the AN *with* binge-eating subtype. This is a novel finding not previously examined in twin research. The positive genetic associations suggest that some genetic loci may be influencing these traits in the same direction. Second, negative  $r_g$ s emerged between the three

non-diagnostic smoking phenotypes and AN *without* binge-eating, but not with the other three eating disorder phenotypes. These negative  $r_g$ s indicate that some of the loci influencing liability to these eating disorder and smoking phenotypes might be shared, but are affecting the liability to these traits in opposite directions. Indeed,  $r_g$ s cannot identify specific loci or underlying mechanisms that contribute to the shared risk. Nevertheless, the results provide initial evidence for differential genetic associations between the liability to varying eating disorder- and substance-use-related phenotypes.

Based on findings from twin studies, we hypothesized that: 1) the strongest SNP-based  $r_g$  would be between eating disorder phenotypes that have binge eating as a core symptom and alcohol use phenotypes; and 2) a significant positive  $r_g$  between eating disorder phenotypes with binge eating as a key symptom and AUD would emerge. In line with these hypotheses, we found a significant genetic association between AUD and AN diagnosis, but not between typical alcohol consumption (i.e., drinks per week) and AN. No twin study has examined genetic associations between AN and alcohol-use-related phenotypes, and previous studies<sup>21,26</sup> using LDSC have not reported significant  $r_g$ s between these traits. That we found a significant association most likely reflects the larger AN sample size in our study (from 3,495 cases and 10,982 controls to 16,992 cases and 55,525 controls), as well as combining two large existing GWAS of AUD, emphasizing the importance of increasing sample sizes for GWAS.

Importantly, the  $r_g$ s between the eating disorder- and substance-use-related phenotypes were robust to conditioning on schizophrenia loci. However, the  $r_g$  between AN and AUD was not robust to the adjustment for major depressive disorder-associated variants. Major depressive disorder is among the most prominent comorbidities in individuals with AN and AUD,<sup>40</sup> and GWAS for both traits document strong  $r_g$ s between major depressive disorder and these

disorders.<sup>19,21,26</sup> Our results indicate that the three disorders share genetic underpinnings. We cannot discount the possibility of a genetic relationship between AN and AUD that is distinct from major depressive disorder; however, much larger sample sizes may be required to detect such an association.

Intriguingly, although we did not detect a significant  $r_g$  for AN *with* binge-eating with AUD, the point estimate for the  $r_g$  between AUD and AN *with* binge-eating was similar to that for AUD and AN diagnosis (0.17 vs. 0.18, respectively) and higher than AUD and AN *without* binge eating (0.01). Sample sizes for these AN subtypes were smaller than for AN diagnosis; however, the two subtypes included approximately equal numbers of cases and controls. Indeed, binge eating was assessed in such a way that we were unable to tease apart purging behaviors, and AN diagnosis is heterogeneous even within subtypes. Therefore, binge eating may be one plausible key component of the observed genetic association. For example, binge eating has been shown to activate brain reward circuitry in a similar manner to substances,<sup>41,42</sup> and administration of naltrexone, an opioid antagonist approved by the U.S. Food and Drug Administration for the treatment of AUD,<sup>43</sup> has been shown to reduce the frequency of binge-eating episodes among individuals with an eating disorder.<sup>44,45</sup> We did not detect a significant  $r_g$  with the bulimia nervosa factor score, although that GWAS was relatively underpowered. Thus, our findings highlight the importance of expanding GWAS to include bulimia nervosa and binge-eating disorder, where a core symptom of both disorders is binge eating, to elucidate whether binge eating is a critical eating disorder symptom in the comorbidity with AUD and to home in on relevant shared mechanisms.

The significant genetic associations between cannabis initiation and AN are novel, yet consistent with the negative genetic association between cannabis use and body mass index, and



with observational<sup>25</sup> and experimental<sup>46,47</sup> studies regarding the role of endocannabinoids in appetite regulation, energy expenditure, stress, and reward. One of the principal psychoactive agents of cannabis, delta-9-tetrahydrocannabinol (THC), a partial agonist of the endogenous cannabinoid 1 (CB1) receptor, is presumed to be orexigenic and may acutely increase appetite and food intake, contributing to its potential role as an appetite stimulant in patients with an anorexia or cachexia syndrome<sup>48</sup> due to a disease (e.g., HIV, AIDS) or in response to treatment (e.g., chemotherapy). An antagonist of the CB1 receptor was previously tested as a highly promising anti-obesity medication (Rimonabant, SR141716), which is particularly relevant since some genes may influence AN and obesity in opposite directions.<sup>21</sup> Further, the endocannabinoid anandamide has been shown to be elevated in individuals with acute AN,<sup>49</sup> indicating disruption in food-related reward and eating behavior regulation. Animal and human studies have also provided initial evidence for the therapeutic effectiveness of cannabinoid agonists in treating eating disorders.<sup>50,51</sup> It is also likely that individuals with high genetic liability to AN are less likely to experiment with a substance that has a documented hyperphagia component. Thus, there is evidence of a complex biological relationship between cannabis use and eating disorders, as well as body mass index.

Finally, the significant negative  $r_g$ s between three tobacco-smoking phenotypes—smoking initiation, current smoking, and cigarettes per day—and AN *without* binge-eating are intriguing, suggesting that AN *without* binge-eating and tobacco-smoking behaviors are alternate expressions of shared mechanisms. Phenotypic studies are inconsistent about the association between the restricting subtype of AN and smoking. Some studies suggest that individuals with restricting AN have a higher prevalence of various smoking phenotypes than controls,<sup>5</sup> whereas other studies indicate no significant difference between the two groups.<sup>6</sup> A recent meta-analysis

did not find differences in the odds of lifetime smoking between individuals with AN and healthy controls,<sup>3</sup> yet the authors did not assess differences by AN subtype. Individuals with AN may smoke as a way to control or lose weight,<sup>52</sup> and temporary weight gain does occur with smoking cessation.<sup>53</sup> However, a positive phenotypic correlation need not be accompanied by a  $r_g$  in the same direction (or genetic contributors to the phenotypic association at all). Still, there is plausible support for the negative  $r_g$ . Although not significant, a negative  $r_g$  between smoking and AN has been reported.<sup>18,21</sup> Notably, our study includes individuals from these earlier reports and extends findings by including larger sample sizes for both AN and smoking phenotypes. Unfortunately, there are no twin studies of AN or AN-like traits and smoking with which to compare findings.

One explanation for the negative genetic association is that it is due to a third, underlying variable influencing both AN *without* binge-eating and smoking. We tested for the potential role of variants associated with major depressive disorder and schizophrenia and found the  $r_g$ s to be robust to those adjustments. In the largest GWAS of smoking phenotypes, positive  $r_g$ s were also observed between smoking initiation and cigarettes per day with multiple cardiometabolic traits, including type 2 diabetes and fasting glucose.<sup>20</sup> These same metabolic traits were negatively genetically correlated with AN.<sup>21,54</sup> Thus, the patterns of  $r_g$ s might point to metabolic, rather than psychiatric, factors in influencing the apparent genetic association between smoking phenotypes and AN. However, the associations could also reflect adoption of unhealthy lifestyles that promote obesity and are correlated with smoking. In addition, the  $r_g$ s between smoking and body mass index, as well as AN and body mass index, may reflect underlying disinhibitory pathways, as variants associated with body mass index show enrichment in the central nervous system.<sup>55</sup> The current approach is not designed to disentangle these putative etiological mechanisms, but

our findings do encourage careful study of the specific relationships between eating and substance use disorders.

Substance use and substance use disorders are partially distinct, and although excessive substance use is a necessary component of substance use disorders, the latter is associated with psychological and physiological impairment related to excess use and aspects of loss of control over the behavior. Consistent with our findings for alcohol, accumulating evidence suggests that genetic liability to other psychiatric traits (e.g., schizophrenia) is strongly correlated with liability to substance use disorders (e.g., AUD) but not substance use (e.g., alcohol consumption).<sup>19-21</sup> Genetic liability to alcohol use has also been correlated with liabilities to psychiatric disorders (e.g., major depressive disorder) in opposite directions depending on level of involvement.<sup>19</sup> However, we did not find similar elevations in  $r_g$ s when contrasting ever smoking and nicotine dependence, nor comparing cannabis initiation to cannabis use disorder. It is possible that the lack of genetic overlap between AN and nicotine dependence, as well as AN and cannabis use disorder, is related to the relatively modest sample size of those discovery GWAS. A similar non-significant  $r_g$  was noted for AUD when the Walters et al.<sup>26</sup> alcohol dependence GWAS was used as the sole source of summary statistics for problem drinking in the current study. Several other explanations for this divergence in findings exist. For instance, for tobacco, the highly addictive nature of nicotine may result in convergence in genomic effects on earlier and later stages of smoking (i.e., a much larger proportion of those who ever smoke become dependent compared with the proportion of those who drink alcohol and develop AUD). For cannabis, given its lower addictive potential, we might have expected stronger associations with cannabis use disorder than with cannabis initiation. In addition to the considerably smaller sample size of the cannabis use disorder GWAS, the association with cannabis initiation could also be attributed

to the small number of cohorts in that discovery GWAS that included individuals with a high likelihood of cannabis use disorder. It is also possible that the relationship between AN and cannabis use is distinct and that earlier, but not later stages of cannabis use are genetically related to liability to AN. Future studies should consider the multi-stage nature of substance use and misuse when examining cross-trait correlations.

This is the largest and most comprehensive assessment of shared genetic risk between eating disorder- and substance-use-related phenotypes, using existing GWAS data from large cohorts (up to ~537,000 individuals per phenotype). We were able to separately assess approximate AN subtypes (i.e., *with* binge-eating vs. *without* binge-eating) to evaluate the extent to which binge eating, in the context of AN, may share genetic risk with substance-use-related phenotypes. Using these large datasets—many of which are publicly available—allows for the rapid development of scientific knowledge regarding the underlying etiology of psychiatric disorder and substance use comorbidity. Nevertheless, some limitations exist. First, sample sizes for the bulimia nervosa factor score and cannabis use disorder GWAS were relatively small compared with the other GWAS, resulting in large standard errors and low power. Second, we were unable to uniformly examine sex differences in these  $r_g$ s. Since the prevalence of eating disorders is higher in women than men and the prevalence of substance use disorders is higher in men than women,<sup>40</sup> it will be important to explore possible sex differences in genetic associations as the GWAS data become available. Notably, we previously did not find evidence for sex differences in the  $r_g$  between binge eating and problem alcohol use.<sup>56</sup> Third, even though we did not detect significant  $r_g$ s for all pairs of traits, it is possible that local genetic associations exist for some of these trait pairs. Such local correlations, for instance, in certain chromosomal regions but not others, particularly when in opposing directions (e.g., a positive local correlation

at one chromosomal location and a negative local correlation at another) might dilute the overall  $r_g$  estimate. Although such a systematic evaluation of each pair of traits is beyond the scope of this report, we did note some support for enrichment of the aggregated genetic covariance in both functional and non-functional genomic regions for several of the significant  $r_g$ s. Finally, SNP coverage was limited in the earlier GWAS of the bulimia nervosa factor score because that study used older genotyping platforms and imputation panels that included fewer SNPs than current imputation panels. The Eating Disorders and Substance Use Disorders Working Groups of the Psychiatric Genomics Consortium are continuously adding samples and releasing data freezes with incrementally larger sample sizes, while collecting information on multiple substances (e.g., opioids). In coming years, the statistical power is expected to increase for AN (including the *with* and *without* binge-eating subtypes), bulimia nervosa, and binge-eating disorder, as well as AUD, nicotine dependence, and cannabis use disorder, from within and outside the Psychiatric Genomics Consortium. This will allow for a more refined assessment of specific eating disorder symptoms, including binge eating, in relation to substance-use-related phenotypes.

In conclusion, findings from this study suggest that the shared sources of variation in liabilities to eating disorder- and substance-use-related phenotypes are not consistent across traits or levels of substance involvement, extending results from twin studies to a genome-wide SNP approach. Despite the typically high co-occurrence of alcohol, tobacco, and cannabis use, and their genetic overlap,<sup>25</sup> the differential patterns seen between the eating disorder- and substance-use-related phenotypes highlight the uniqueness and complexity of their shared etiology. Potential clinical implications include watching for the emergence of symptoms of one disorder (e.g., AN) while being treated for the other behavior (e.g., alcohol use disorder), and understanding that, for example, women with AN who use nicotine may not be able to quit

successfully both because they are afraid of gaining weight and they have high genetic susceptibility for smoking via the shared genetic risk between AN and smoking-related traits. Additional research using contemporary genomic methods, such as cross-disorder association studies, could identify the specific loci contributing to this comorbidity. Future research that combines genome-wide data with measured environmental constructs, such as trauma,<sup>9</sup> that may increase risk for this comorbidity could enhance the prediction, prevention, and treatment of co-occurring eating disorder- and substance-use-related traits.

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### *Eating Disorders Working Group of the Psychiatric Genomics Consortium (PGC-ED)*

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***Substance Use Disorders Working Group of the Psychiatric Genomics Consortium (PGC-SUD)***

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***Data Access***

This manuscript was a joint collaboration between the Eating Disorders and Substance Use Disorders Working Groups of the Psychiatric Genomics Consortium. These data can be found at <https://www.med.unc.edu/pgc/data-index/>. Additional datasets included in this study were obtained multiple ways. We recieved summary statistics directly from the first author of the primary GWAS manuscript for the bulimia nervosa factor score (Australian Twin Registry), alcohol use disorder (Million Veteran Program), nicotine dependence (multiple samples), and cannabis initiation (International Cannabis Consortium and UK Biobank). Summary statistics for drinks per week, smoking initiation, smoking cessation, and cigarettes per day (GSCAN) were downloaded from <https://conservancy.umn.edu/handle/11299/201564> on March 7, 2019. Summary statistics for cannabis use disorder (iPSYCH) were downloaded from <https://ipsych.dk/forskning/downloads/> on June 27, 2019.

### **Competing Financial Interests**

The authors report the following potential competing interests. O. Andreassen received a speaker's honorarium from Lundbeck. G. Breen received grant funding and consultancy fees in preclinical genetics from Eli Lilly, consultancy fees from Otsuka, and has received honoraria from Illumina. C. Bulik served on Shire Scientific Advisory Boards, is a consultant for Idorsia, and receives author royalties from Pearson. D. Degortes served as a speaker and on advisory boards, and has received consultancy fees for participation in research from various pharmaceutical industry companies including: AstraZeneca, Boehringer, Bristol Myers Squibb, Eli Lilly, Genesis Pharma, GlaxoSmithKline, Janssen, Lundbeck, Organon, Sanofi, UniPharma, and Wyeth; he has received unrestricted grants from Lilly and AstraZeneca as director of the Sleep Research Unit of Eginition Hospital (National and Kapodistrian University of Athens, Greece). J. Hudson has received grant support from Shire and Sunovion, and has received consulting fees from DiaMentis, Shire, and Sunovion. A. Kaplan is a member of the Shire Canadian Binge-Eating Disorder Advisory Board and was on the steering committee for the Shire B/educated Educational Symposium: June 15-16, 2018. J. Kennedy served as an unpaid member of the scientific advisory board of AssurexHealth Inc. M. Landén declares that, over the past 36 months, he has received lecture honoraria from Lundbeck and served as scientific consultant for EPID Research Oy. No other equity ownership, profit-sharing agreements, royalties, or patent. S. Scherer is a member of the scientific advisory board for Deep Genomics. P. Sullivan is on the Lundbeck advisory committee and is a Lundbeck grant recipient; he has served on the scientific advisory board for Pfizer, has received a consultation fee from Element Genomics, and a speaker reimbursement fee from Roche. J. Treasure has received an honorarium for participation in an EAP meeting and has received royalties from several books from

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### **Authors Contribution**

M. Munn-Chernoff, C. Bulik, and A. Agrawal were responsible for the study concept and design. M. Munn-Chernoff, E.C. Johnson, and Y.-L. Duan performed the statistical analyses, and J. Coleman, R. Walters, and Z. Yilmaz assisted with the data analysis. M. Munn-Chernoff, E.C. Johnson, Y.L. Duan, J. Coleman, L. Thornton, R. Walters, Z. Yilmaz, J. Baker, C. Hübel, J. Kaprio, H. Edenberg, C. Bulik, and A. Agrawal assisted with interpretation of findings. T. Wade facilitated access to and interpretation of the summary statistics for the bulimia nervosa factor score. H. Kranzler, J. Gelernter, and H. Zhou facilitated access to and interpretation of the Million Veteran Program summary statistics for AUD. D. Hancock facilitated access to and interpretation of the summary statistics for nicotine dependence. M. Munn-Chernoff, E.C. Johnson, L. Thornton, C. Bulik, and A. Agrawal drafted the manuscript. All remaining authors provided data for this study and consulted on the analytic plan. All authors critically reviewed the content and approved the final version for publication.

### References

1. Root TL, Pisetsky EM, Thornton L, Lichtenstein P, Pedersen NL, Bulik CM. Patterns of co-morbidity of eating disorders and substance use in Swedish females. *Psychol Med* 2010,40:105-115.
2. Gadalla T, Piran N. Co-occurrence of eating disorders and alcohol use disorders in women: A meta analysis. *Arch Womens Ment Health* 2007,10:133-140.
3. Solmi M, Veronese N, Sergi G, et al. The association between smoking prevalence and eating disorders: A systematic review and meta-analysis. *Addiction* 2016,111:1914-1922.
4. Wiederman MW, Pryor T. Substance use among women with eating disorders. *Int J Eat Disord* 1996,20:163-168.
5. Krug I, Treasure J, Anderluh M, et al. Present and lifetime comorbidity of tobacco, alcohol and drug use in eating disorders: A European multicenter study. *Drug Alcohol Depend* 2008,97:169-179.
6. Anzengruber D, Klump KL, Thornton L, et al. Smoking in eating disorders. *Eat Behav* 2006,7:291-299.
7. Duncan AE, Neuman RJ, Kramer JR, Kuperman S, Hesselbrock VM, Bucholz KK. Lifetime psychiatric comorbidity of alcohol dependence and bulimia nervosa in women. *Drug Alcohol Depend* 2006,84:122-132.
8. Franko DL, Keshaviah A, Eddy KT, et al. A longitudinal investigation of mortality in anorexia nervosa and bulimia nervosa. *Am J Psychiatry* 2013,170:917-925.
9. Center on Addiction and Substance Abuse. Food for thought: Substance abuse and eating disorders. Columbia University (ed), New York, NY: The National Center on Addiction and Substance Abuse at Columbia University; 2003,1-83.

10. Munn-Chernoff MA, Baker JH. A primer on the genetics of comorbid eating disorders and substance use disorders. *Eur Eat Disord Rev* 2016,24:91-100.
11. Baker JH, Mazzeo SE, Kendler KS. Association between broadly defined bulimia nervosa and drug use disorders: Common genetic and environmental influences. *Int J Eat Disord* 2007,40:673-678.
12. Baker JH, Mitchell KS, Neale MC, Kendler KS. Eating disorder symptomatology and substance use disorders: Prevalence and shared risk in a population based twin sample. *Int J Eat Disord* 2010,43:648-658.
13. Rhee SH, Hewitt JK, Young SE, Corley RP, Crowley TJ, Stallings MC. Genetic and environmental influences on substance initiation, use, and problem use in adolescents. *Arch Gen Psychiatry* 2003,60:1256-1264.
14. Heath AC, Bucholz KK, Madden PA, et al. Genetic and environmental contributions to alcohol dependence risk in a national twin sample: Consistency of findings in women and men. *Psychol Med* 1997,27:1381-1396.
15. True WR, Heath AC, Scherrer JF, et al. Genetic and environmental contributions to smoking. *Addiction* 1997,92:1277-1287.
16. van den Bree MB, Johnson EO, Neale MC, Pickens RW. Genetic and environmental influences on drug use and abuse/dependence in male and female twins. *Drug Alcohol Depend* 1998,52:231-241.
17. Bulik-Sullivan BK, Loh PR, Finucane HK, et al. LD Score regression distinguishes confounding from polygenicity in genome-wide association studies. *Nat Genet* 2015,47:291-295.

18. Bulik-Sullivan B, Finucane HK, Anttila V, et al. An atlas of genetic correlations across human diseases and traits. *Nat Genet* 2015,47:1236-1241.
19. Kranzler HR, Zhou H, Kember RL, et al. Genome-wide association study of alcohol consumption and use disorder in 274,424 individuals from multiple populations. *Nat Commun* 2019,10:1499.
20. Liu M, Jiang Y, Wedow R, et al. Association studies of up to 1.2 million individuals yield new insights into the genetic etiology of tobacco and alcohol use. *Nat Genet* 2019,51:237-244.
21. Watson HJ, Yilmaz Z, Thornton LM, et al. Genome-wide association study identifies eight risk loci and implicates metabo-psychiatric origins for anorexia nervosa. *Nat Genet* 2019,51:1207-1214.
22. Gregorowski C, Seedat S, Jordaan GP. A clinical approach to the assessment and management of co-morbid eating disorders and substance use disorders. *BMC Psychiatry* 2013,13:289.
23. Wade TD, Gordon S, Medland S, et al. Genetic variants associated with disordered eating. *Int J Eat Disord* 2013,46:594-608.
24. Hancock DB, Guo Y, Reginsson GW, et al. Genome-wide association study across European and African American ancestries identifies a SNP in DNMT3B contributing to nicotine dependence. *Mol Psychiatry* 2017,23:1-9.
25. Pasman JA, Verweij KJH, Gerring Z, et al. GWAS of lifetime cannabis use reveals new risk loci, genetic overlap with psychiatric traits, and a causal influence of schizophrenia. *Nat Neurosci* 2018,21:1161-1170.



26. Walters RK, Polimanti R, Johnson EC, et al. Transancestral GWAS of alcohol dependence reveals common genetic underpinnings with psychiatric disorders. *Nat Neurosci* 2018,21:1656-1669.
27. Demontis D, Rajagopal VM, Thorgeirsson TE, et al. Genome-wide association study implicates CHRNA2 in cannabis use disorder. *Nat Neurosci* 2019,22:1066-1074.
28. Fairburn CG, Cooper Z. The Eating Disorder Examination. In: Fairburn CG, Wilson GT, eds.: *Binge Eating: Nature, Assessment and Treatment*, New York: Guilford Press 1993,317-359.
29. Benjamini Y, Hochberg Y. Controlling the false discovery rate: A practical and powerful approach to multiple testing. *J Royal Statist Soc, Series B* 1995,57:449-518.
30. Lu Q, Li B, Ou D, et al. A powerful approach to estimating annotation-stratified genetic covariance via GWAS summary statistics. *Am J Hum Genet* 2017,101:939-964.
31. Lu Q, Hu Y, Sun J, Cheng Y, Cheung KH, Zhao H. A statistical framework to predict functional non-coding regions in the human genome through integrated analysis of annotation data. *Sci Rep* 2015,5:10576.
32. Lu Q, Powles RL, Abdallah S, et al. Systematic tissue-specific functional annotation of the human genome highlights immune-related DNA elements for late-onset Alzheimer's disease. *PLoS Genet* 2017,13:e1006933.
33. Lu Q, Powles RL, Wang Q, He BJ, Zhao H. Integrative tissue-specific functional annotations in the human genome provide novel insights on many complex traits and improve signal prioritization in genome wide association studies. *PLoS Genet* 2016,12:e1005947.

34. Encode Project Consortium. An integrated encyclopedia of DNA elements in the human genome. *Nature* 2012,489:57-74.
35. Roadmap Epigenomics Consortium, Kundaje A, Meuleman W, et al. Integrative analysis of 111 reference human epigenomes. *Nature* 2015,518:317-330.
36. Zhu Z, Zheng Z, Zhang F, et al. Causal associations between risk factors and common diseases inferred from GWAS summary data. *Nat Commun* 2018,9:224.
37. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nat Genet* 2018,50:668-681.
38. Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014,511:421-427.
39. Yengo L, Yang J, Visscher PM. Expectation of the intercept from bivariate LD score regression in the presence of population stratification. *bioRxiv* 2018:  
<https://doi.org/10.1101/310565>.
40. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders (5<sup>th</sup> ed)*. Arlington, Virginia: American Psychiatric Publishing, 2013. 947 p.
41. Kaye WH, Wierenga CE, Bailer UF, Simmons AN, Wagner A, Bischoff-Grethe A. Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa? *Biol Psychiatry* 2013,73:836-842.
42. Volkow ND, Wang GJ, Tomasi D, Baler RD. The addictive dimensionality of obesity. *Biol Psychiatry* 2013,73:811-818.
43. Kranzler HR, Soyka M. Diagnosis and pharmacotherapy of alcohol use disorder: A review. *JAMA* 2018,320:815-824.

44. Stancil SL, Adelman W, Dietz A, Abdel-Rahman S. Naltrexone reduces binge eating and purging in adolescents in an eating disorder program. *J Child Adolesc Psychopharmacol* 2019;29:721-724.
45. Jonas JM, Gold MS. The use of opiate antagonists in treating bulimia: A study of low-dose versus high-dose naltrexone. *Psychiatry Res* 1988;24:195-199.
46. Di Marzo V, Matias I. Endocannabinoid control of food intake and energy balance. *Nat Neurosci* 2005;8:585-589.
47. Volkow ND, Hampson AJ, Baler RD. Don't worry, be happy: Endocannabinoids and cannabis at the intersection of stress and reward. *Annu Rev Pharmacol Toxicol* 2017;57:285-308.
48. Reuter SE, Martin JH. Pharmacokinetics of cannabis in cancer cachexia-anorexia syndrome. *Clin Pharmacokinet* 2016;55:807-812.
49. Monteleone P, Maj M. Dysfunctions of leptin, ghrelin, BDNF and endocannabinoids in eating disorders: Beyond the homeostatic control of food intake. *Psychoneuroendocrinology* 2013;38:312-330.
50. Avraham Y, Paturski I, Magen I, Vorobiev L, Berry EM. 2-Arachidonoylglycerol as a possible treatment for anorexia nervosa in animal model in mice. *Brain Res* 2017;1670:185-190.
51. Andries A, Frystyk J, Flyvbjerg A, Stoving RK. Dronabinol in severe, enduring anorexia nervosa: A randomized controlled trial. *Int J Eat Disord* 2014;47:18-23.
52. White MA. Smoking for weight control and its associations with eating disorder symptomatology. *Compr Psychiatry* 2011;53:403-407.

53. Filozof C, Fernandez Pinilla MC, Fernandez-Cruz A. Smoking cessation and weight gain. *Obes Rev* 2004,5:95-103.
54. Duncan L, Yilmaz Z, Gaspar H, et al. Significant locus and metabolic genetic correlations revealed in genome-wide association study of anorexia nervosa. *Am J Psychiatry* 2017,174:850-858.
55. Goodarzi MO. Genetics of obesity: What genetic association studies have taught us about the biology of obesity and its complications. *Lancet Diabetes Endocrinol* 2018,6:223-236.
56. Munn-Chernoff MA, Duncan AE, Grant JD, et al. A twin study of the association between alcohol dependence, binge eating, and compensatory behaviors. *J Stud Alcohol Drugs* 2013,74:664-673.

**Table 1. Eating disorder-related phenotype descriptions.**

Phenotype	Definitions
Anorexia nervosa (AN) <sup>a</sup>	<p>Diagnostic criteria included:</p> <ol style="list-style-type: none"> <li>1. Body mass index less than minimally expected</li> <li>2. Intense fear of gaining weight</li> <li>3. Weight or shape disturbance, undue influence of weight or shape, or denial of the seriousness of the disorder</li> </ol>
AN <i>with</i> binge-eating <sup>b</sup>	<p>Individuals with AN who also engaged in binge eating episodes, defined as eating a large amount of food in a short period of time while having a sense of loss of control over the eating episode. The binge eating episodes must have occurred at least twice a week for three months.</p>
AN <i>without</i> binge-eating <sup>b</sup>	<p>Individuals with AN who did not engage in binge eating episodes.</p>
Bulimia nervosa (BN) <sup>c</sup> factor	<p>Derived from a factor analysis that included the following items:</p> <ol style="list-style-type: none"> <li>1. Reporting self-induced vomiting to control body weight</li> <li>2. Reporting suffering from or being treated for binge eating</li> <li>3. Reporting suffering from or being treated for bulimia</li> </ol>

**Note:** <sup>a</sup>A fourth diagnostic criterion for AN includes amenorrhea. However, amenorrhea was excluded as a required criterion for cases in the Psychiatric Genomics Consortium datasets since it is no longer a diagnostic criterion in the DSM-5. <sup>b</sup>The DSM and ICD include two subtypes of anorexia nervosa (AN)—a binge-eating/purging subtype and a restricting subtype. Although it would have been ideal to examine differences between the AN binge-eating/purging subtype and AN restricting subtype, this was not possible with current Psychiatric Genomics Consortium data. However, there was sufficient information about presence or absence of binge eating, which resulted in creating the AN *with* binge-eating and AN *without* binge-eating subtypes. <sup>c</sup>Bulimia nervosa is defined as: 1) recurrent episodes of binge eating; 2) recurrent inappropriate compensatory behaviors (e.g., self-induced vomiting, laxative use) to prevent weight gain; 3) the binge eating and inappropriate compensatory behaviors occurring an average of twice a week for three months; 4) having undue influence of body weight and shape; and 5) disturbance not occurring during AN.

**Table 2. Details of samples included in analyses.**

Study	Sample/Consortium	Phenotype(s)	Definition	Sample Size (cases / controls if binary)	Number of SNPs in summary statistics file
<i>Eating Disorder Phenotype</i>					
Watson et al. (2019)	PGC-ED	1. Anorexia nervosa	DSM-III-R, DSM-IV, ICD-8,	16,992 / 55,525	8,219,102
		2. Anorexia nervosa <i>with</i> binge-eating	ICD-9, ICD-10, or self-reported anorexia nervosa	2,381 / 10,249	8,982,440
		3. Anorexia nervosa <i>without</i> binge-eating		2,262 / 10,254	8,671,192
Wade et al. (2013)	Australian Twin Registry	Bulimia nervosa factor	Eating Disorder Examination	151 / 2,291	6,150,213
<i>Substance Use-Related Phenotype</i>					
Kranzler et al. (2019)	MVP	Alcohol use disorder	ICD-9 or ICD-10	34,658 / 167,346	6,895,251
Walters et al. (2018)	PGC-SUD	Alcohol dependence	DSM-IV	8,485 / 20,272	9,271,145
Liu et al. (2019)	GSCAN	1. Drinks per week*	Average number of drinks each week	537,349	11,916,707
		2. Smoking initiation	Ever vs. never regular smoker	311,629 / 321,173	11,733,344
		3. Current smoking <sup>a</sup>	Current vs. former smokers	92,573 / 220,248	12,197,133

**Table 2 (cont). Details of samples included in analyses.**

Study	Sample/Consortium	Phenotype(s)	Definition	Sample Size (cases / controls if binary)	Number of SNPs in summary statistics file
		4. Cigarettes per day*	Average number of cigarettes smoked per day	263,954	12,003,613
Hancock et al. (2017)	14 samples	Nicotine dependence**	Mild (FTND score 0-3), Moderate (FTND score 4-6), or Severe (FTND score 7-10)	14,184 (Mild) 9,206 (Moderate) 5,287 (Severe)	10,622,668
Pasman et al. (2018)	ICC UK Biobank	Cannabis initiation	Lifetime cannabis use	43,380 / 118,702	11,733,371
Demontis et al. (2019)	iPSYCH	Cannabis use disorder	ICD-10	2,387 / 48,985	8,969,939

**Note:** SNPs=single nucleotide polymorphisms; PGC-ED=Eating Disorders Working Group of the Psychiatric Genomics Consortium; DSM=Diagnostic and Statistical Manual; ICD=International Classification of Diseases; PGC-SUD=Substance Use Disorders Working Group of the Psychiatric Genomics Consortium; MVP=Million Veteran Program; GSCAN=GWAS & Sequencing Consortium of Alcohol and Nicotine use; FTND=Fagerström Test of Nicotine Dependence; ICC=International Cannabis Consortium; iPSYCH=Lundbeck Foundation Initiative for Integrative Psychiatric Research. \*Treated as a continuous phenotype. \*\*Treated as an



ordinal phenotype. <sup>a</sup>In Lui et al. (2019), the phenotype is labeled as “smoking cessation”. It was renamed as “current smoking” to reflect the coding scheme and for ease in comparing across all smoking phenotypes.

**Figure 1. Genetic correlations between eating disorder subtypes and substance-use-related phenotypes.** # indicates known or potential sample overlap with UK Biobank; & indicates known sample overlap with iPSYCH. Starred values denote significant genetic correlations after correcting for multiple comparisons using False Discovery Rate ( $n$  tests=66;  $q<0.05$ ).



